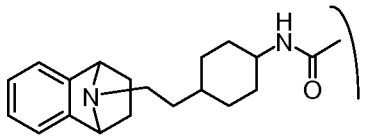
REMARKS

Claims 1 to 4, 6, 8 to 10, and 13 to 31 are in the application. Claims 4 and 6 have been amended. Claims 21 to 26 have been added. Support for the amendment and newly added claims lies in the claims as originally filed, the working examples or the specification on page 4, lines 24 to 30; page 5, lines 1 to 3; page 61, lines 18 to 30. No new matter is believed added. Applicants reserve their right to file continuation or divisional applications on all cancelled or deleted subject matter.

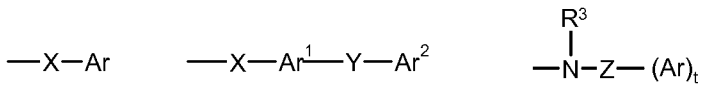
Rejection under 35 USC §112

Claims 1 to 4, 6, 8 to 10, and 13 to 20 are rejected under 35 USC §112, first paragraph as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The present application is a §371 national stage entry of a PCT application. No lack of unity was found during examination of the PCT application. The Examiner requested an election of a single disclosed species in the previous restriction requirement. The compound of Example 11 was elected and presumably examined. There is a "core" pharmacophore for the present genus disregarding various stereochemistry and the single or double bond for G1 in the ring:



The remaining substituents become the R^2 moiety which can be selected from 3 formulas:



(d) (e) (f)

A compound of Formula d was elected for examination. Formula (e) is similar to formula (d) in hat the X-Ar1 portion of the moiety is encompassed by formula (d) –X-Ar. The Ar term being broader in scope than the Ar^1 moiety. Consequently, all searching of formula (d) would by necessity pick up compound of Formula (e). Compounds of Formula (f) form a urea linkage. However, Formula (d) when X is nitrogen, also forms a urea linkage. Consequently, again the core substitutions reduce themselves in variability within each of these formulas and it is not believed that any additional burdens of searching have been

placed upon the Examiner. No prior art has been cited by the Examiner, and no further discussion regarding the genus which has been searched has been made. Consequently, Applicants believe that the full scope of the compounds contained within Formula (I) has been searched.

It should be noted that the specification not only contains synthetic examples for 135 distinct compounds, but also six (6) schemes describe how to making compounds of Formula (I). Compounds wherein R2 is a compound of formula (d), (e) and (f) are all exemplified. Consequently, Applicants believe that the specification teaches one of ordinary skill in the art how to make, without "undue experimentation" the full scope of the claimed invention herein. Further it should be noted that the claims are not broader in scope than the specification.

"The enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003), citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Clearly, one of ordinary skill in the art would be able to synthesize a wide range compounds of Formula (I) which are within the scope of the genus.

The specification also provides details on what the compounds are useful for, e.g. treatment of respiratory-tract disorders (page 61, lines 5 to 8; and orally for other anticholinergic diseases, such as GI-tract disorders (page 61, lines 8 to 11) and urinary tract disorders (page 61, lines 11 to 15). These diseases, would be recognized by one of ordinary skill in the art as common to anticholinergic therapy.

The compounds are clearly directed in the specification towards delivery to the lungs (pages 61, lines 17 to end to page 66, line 27) whether it be via the oral inhalation route or nasal delivery. In fact there are four (4) examples of nasal formulations presented, as well as a significant discussion on the various inhalers and some formulation details therein. The use of these types of devices and surrounding formulations are also well known and described in the art. Consequently, it is believed that one of ordinary skill in the art would therefore be provided with sufficient information to also be able to use the compounds of Formula (I).

It should be noted that far fewer than 40 working examples were sufficient to enable the broad claims in *In re Wands*, 858 F.2d at 735, 8 U.S.P.Q.2d at 1402.

More importantly, there may not even be a requirement to have <u>any</u> working embodiments in order to satisfy the requirements of § 112, first paragraph, even in the

chemical arts, as evidenced by the decision in *In re Strahilevitz*, 668 F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982). In this case, Applicants had described the invention with specificity, but had not disclosed even a single operative embodiment. The court acknowledged that the claims at issue were extremely broad, yet the court reversed the Board's holding of nonenablement, having been persuaded by Strahilevitz that the invention consisted in combining known prior art techniques. Pointing out that § 112 does not require working examples (though they may be desirable in complex technologies), the court found the broad claims enabled throughout their scope. In *Strahilevitz*, Applicants were able to obtain broad claims to methods for removing haptens from blood, despite the fact that no working examples were disclosed, because the evidence of record established that the prior art had taught methods that, when combined together according to the teachings of the specification, could be used to make the claimed invention.

The MPEP 2164.01(c) on How to Use the Claimed Invention also clearly contemplates that a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, and that 25 USC §112 is thereby satisfied. The state of the art, taken with Applicants specification is sufficient within the context of M3 receptors antagonists to be enabled.

By law a patent application is presumptively enabled when filed. That is, during examination, "[a]s a matter of Patent Office practice . . . a specification . . . must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d at 223, 169 U.S.P.Q. at 369.

Moreover,

> . . . it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224, 169 U.S.P.Q. at 369-70.

Since the PTO bears the initial burden of challenging the presumed utility of an invention, it must produce sufficient evidence that one of ordinary skill in the art would have reason to doubt the claimed utility of the invention.

One of skill in the art, in combination with the submitted references as well as the state of the art would not question the claimed utility of the compounds described and claimed herein. The nature of the applicants' invention itself would also not tend to cause one skilled in the art to doubt its usefulness. In fact, the very compounds cited by the Examiner in the Office Action, Ipartropium, Oxitropium and Tiotropium are all muscarinic acetylcholine antagonists (See Office Action, Page 5, 1rst full ¶).

The Examiner states that "These compounds show a very tight structure-activity relationship" (quoting an excerpt from Goodman & Gilman and that "an intact ester of tropine and tropic acid is essential for antimuscarinic action, since neither the free acid nor the base exhibits significant antimuscarinic activity" (See Office Action, Page 5, 1rst full ¶, and page 6, lines 1 and 2). It is unclear what the point of this is. These three compounds do not share a common pharmacophore with Applicants compounds. Therefore, any comments about the structure-activity relationship (SAR) for those compounds and the SAR for the present genus is not relevant. Also, it appears from the comment that the free acid and the base are active, e.g. they do posses antimuscarinic activity. There is no expectation by the skilled artisan that all the compounds within a genus will possess, to use the Examiners terminology, "significant" activity. It is enough that they have such activity and it is left to further research and development efforts to select a "developable" candidate compound which a sufficient level of *in vivo* activity, coupled with a preferred toxicological profile to go forward with. The courts have long recognized that this occurs much later than the earlier stage discovery of such compounds.

In re Brana, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (CAFC 1995) is one of these cases wherein the Court emphasized that properly patented pharmaceutical inventions usually require further research and development. Thus, the point at which an invention becomes useful enough for a patent will often be long before it is ready for human use. To hold otherwise, noted the Court, would raise the costs of obtaining patent protection for new inventions and remove the incentive to fully research and develop vital drugs and potential cures. *Id* at 1567-68.

The Examiner comments on Point 1, page 4, 2nd paragraph there under in the Office action:

"The relative skill of those in the art if high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience."

Applicants question the Examiners ability to determine the level of the skilled artisan in this instance. Little judicial determination has occurred to provide direction as to what is the appropriate level of skill in the art. In this instance it is merely the Examiner's conjecture that this is the appropriate level of skill.

Another issue if the Examiner's rejection of all the claims under 35 USC §112 for enablement primarily it appears because there is a lack of "experimental evidence commensurate in scope with the claims." (See Office Action, page 7, 1rst ¶).

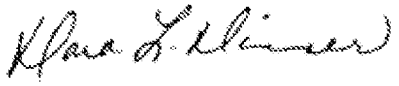
As noted above, there is no requirement that any experimental evidence be submitted in order for the specification to be enabled. This appears to be an incorrect interpretation of chemical patent law. The MPEP in 2164.02 clearly considers this and comments there that "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation", citing In Re Borkowski, 164 USPQ 62, 645 (CCPA 1970). There is not a lack of working examples, 135 compounds are described in the specification. Biological Assays are described in the specification. Simply because Applicants did not provide specific data for each of the compounds does not mean absent some specific finding by the Examiner that the 135 compounds don't possess antimuscarinic activity. What the potency of these compounds are is not the point. It is Applicants determination, illustrated by the filing of the specification, that the compounds of Formula (I) do in fact possess this well known and recognized utility.

The specification clearly provides 2 biological assays, on *in vitro* and one *in vivo* which direct the skilled artisan on how to determine whether a compound has inhibitory action on the muscarinic receptors, an in particular the M3 receptor. See pages 59, lines 6 to 17; page 60, lines 1 to 34; and page 61, lines 1 to 4. This is noted by the Examiner on page 6, point 3 of the office action. The Examiner comments that "no experimental data for any of the compound claimed, including the elected species, if offered."

The basic precept in patent law is that the requirements of § 112 are satisfied only if the disclosure reasonably apprises the ordinary artisan, in light of what is well-known in the art, how to make and how to use a claimed invention *throughout its scope*.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



Dara L. Dinner
Agent for Applicant
Registration No. 33,680

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-6150
Facsimile (610) 270-5090